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EXAMINER	
LUKTON, DAVID	

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1653	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/492,392	Applicant(s) Commercon
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 9, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *17-33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *17-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 15 (filed 4/9/02), claims 17 and 25 have been amended. Claims 17-33 remain pending.

Applicants' arguments filed 4/9/02 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have begun by arguing that when a pharmacological use has been asserted, and at the same time no data has been provided, *In re Brana* confers upon applicants "immunity" from an enablement rejection, as long as applicants can argue that the claimed compounds are "structurally similar" to compounds that have been shown by others to exhibit a pharmacological use. First, the cited passage refers to "utility", rather than enablement, and so it may be dismissed on this basis alone, since no rejection under §101 has been imposed. Second, in *Brana*, the applicants did provide *in vitro* data, and so the Court

never had to decide the question of whether an applicant can be required to provide evidence of enablement in cases where no data whatsoever has been provided. Thus, *Brana* confers no "immunity" from this ground of rejection. Morever, in the *Brana* case, there was no claim drawn to a "pharmaceutical composition".

Applicants have next argued that what really matters is whether one would have reason to doubt the asserted utility. However, this is a moot issue, since no rejection under §101 has been imposed. Next, applicants make further arguments as to why the imposition of a §101 rejection would be inappropriate. However, this is also a moot issue, since no rejection under §101 has been imposed.

Next, applicants have argued that the specification provides some guidance as to how to "administer" the claimed compounds. This point is not in dispute, but neither is it relevant to the discussion. Any compound can be administered; it does not follow therefrom, however, that all compounds are enabled. Next, applicants have argued that because the specification has proposed a dosage range for an unidentified disease, it follows therefrom that the compounds are enabled. However, one can take a given compound which has been shown unequivically to lack any antibacterial activity whatsoever, and then assert that symptoms of tuberculosis, anthrax, or septicemia will be substantially relieved by administering the compound at dosage "X". However, the mere assertion that these disorders can be treated by administering dosage "X" does not transform an inactive

compound into an active one. Accordingly, the assertion regarding dosages does not contribute to a showing of enablement. Moreover, the first question is not whether humans (stricken with a bacterial disease) can derive benefit from the claimed compounds; rather, the initial question is whether any of the compounds will exhibit any efficacy in a petri dish. There is no evidence that this is the case.

Applicants have also pointed to page 11 line 20+, where the following is recited:

"they synergize the antimicrobial activity of pristinamycin".

However, this phrase is very ambiguous, and subject to interpretation. First, it is not clear what "they" refers to. "They" could refer to a mixture of one of the compounds of claim 17 in combination with a "Group B streptogramin". Thus, even if one chooses to interpret the passage in question as an assertion that "they" are synergistic, all of the efficacy (if any) could still reside in the "Group B streptogramin", rather than the compounds of claim 17. Second, it is not clear what is meant by "synergizing". Does this mean that the effective dosage of pristinamycin is reduced when administered in combination with acompound of claim 17 and a "Group B streptogramin"...? If so, this is not necessarily in accord with the asserted utility, which is that of inhibiting bacterial growth. There are many excipients, which are pharmacologically inactive by themselves, but which can enhance the activity of pharmacologically active compounds. Such enhancement can certainly be "useful". But if the claimed compounds do not exhibit antibacterial in and of themselves, enablement is

lacking. Third, the presence or absence of "synergy" is something that would have to be subject to scrutiny. For example, suppose that an investigator has two rats, both infected with *S. aureus*, and two compounds, designated "X" and "Y". Compound "X" has been shown definitively to exhibit antibacterial activity, and compound "Y" is untested, and may be inactive. The researcher then administers compound "X" to the first rat, and a mixture of "X" and "Y" to the second. The result is that the first rat dies, and the second rat lives. What would such an experiment mean? Suppose next that the researcher infects forty rats with *S. aureus*, and adminsters compound "X" to rats #1-20, and administers a mixture of "X" and "Y" to rats #21-40. The result is that 12 of rats #1-20 survive, and just 11 of rats #21-40. Is there "synergy"....? Finally, the researcher tests compound "Y" against a colony of *S. aureus* (in a petri dish) and discovers that compound "Y" is entirely inactive. Thus, based on the first experiment (on two rats), a person with no knowledge of probability, statistics, or microbiology might be inclined to believe that compound "Y" is "synergistic". A more experienced scientist, however, would hold a different view. The point is that one could reach a conclusion of synergy erroneously, especially if the experiments are based on a statistical analysis of numbers of surviving versus dying animals. This is not to say that applicants are "wrong", or that they are "right" (with regard to synergy), only that given the situation, a mere assertion of synergy with nothing more, is not particularly meaningful.

Applicants have also argued that the examiner has not provided "any reason for doubting applicants' aserted antibacterial activity", and that the examiner "alleges without legal authority that ...undue experimentation would be required" . However, the legal authority is *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988). Moreover, the Court has reaffirmed the principals therein in a more recent case (*Enzo Biochem v. Calgene* **52** USPQ2d 1129, 2000). As indicated previously, the factors for evaluating the need for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As indicated previously, the following references disclose either or both of the following: (a) compounds that failed to inhibit bacteria and (b) that compounds which failed to inhibit bacteria were minor structural variants of compounds that do inhibit bacteria:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

In response to the foregoing, applicants have argued in effect that because the label "streptogramin" has not been applied to any of the compounds in the references, it remains the case that one can look at the structure of a "streptogramin", and thereby determine its activity. However, this argument is found not persuasive. The fact is that, where antibacterial activity is concerned, structure/activity relationships are unpredictable. There is no reason to expect that streptogramins would constitute the sole exception to the generalization that structure/activity relationships are unpredictable, and minor changes in structure can eliminate activity. Applicants have also missed the point of the "Fudou" reference; it is true that the reference teaches antifungal activity, but that is not the point. The point is that is teaches the "failure" of the compound to inhibit bacterial growth. This supports the examiner's contention that, for those searching for new antibacterial agents, one cannot merely look at the structure of a compound and determine its activity thereby.

The next issue concerns claims 32-33. These claims are drawn to "pharmaceutical compositions". The term "pharmaceutical" pertains to the disposition and formulation of drugs. As such, there is an implied assertion of therapeutic efficacy in the treatment of diseases. Applicants have stated that they "do not recite any element in the claims themselves regarding treatment of any particular disease. Therefore, applicants are not obliged to entertain the examiner's request with respect to particular diseases". However, because of the term "pharmaceutical", the implication is that the compounds are intended for use in the treatment of diseases that are caused by bacteria. Perhaps a contrast would be useful. Suppose that a researcher has obtained *in vitro* data on a given compound (compound "Z"). The researcher has a theory about how the physiology of the rat might change if compound "Z" were administered. The researcher then combines compound "Z" with a carrier such as saline, or cellulose or glycerol, and prepares to administer compound "Z" . Is it really the case that, merely by combining compound "Z" with the carrier the researcher is in possession of a "pharmaceutical composition"...?

As it happens, diseases caused by bacteria include the following:

> Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever

Applicants have not shown even in vitro efficacy, and so there is no reason to expect that any of the foregoing diseases could be successfully treated.

Continuing with the issue of "pharmaceutical compositions" (claims 32-33), the following references teach "failure" in the treatment of ulcers that are caused by *Helicobacter*; as such, they contribute to the assertion of "unpredictability" that is made by the examiner:

Phillips, (*Helicobacter* 6, 151, 2001);

Pilotto (*Digestive and Liver Disease* 32 (8) 667-72, 2000);

Leung (*Expert Opin Pharmacother* 1 (3) 507-14, 2000).

In addition, Otvos "Insect peptides with improved protease-resistance protect mice against bacterial infection" (Protein Science **9** (4) 742-9, 2000) discloses one peptide that is active *in vitro* but not *in vivo* (due to the rapid decomposition in mammalian sera). Again, *in vitro* data are not necessarily predictive of *in vivo* efficacy. In addition, there is the problem of antibiotic resistance. Presumably applicants are aware of this, but if not, the following two articles discuss this matter:

Liu (*Advances in Experimental Medicine and Biology* 455, 387 1999)

Monroe (*Current Opinion in Microbiology* 3(5) 496-501, 2000).

Accordingly, (a) one cannot predict antibacterial activity merely by viewing a structure, (b)

"undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth, and (c) even if it were true that the compounds exhibited antibacterial activity in vitro, "undue experimentation" would be required to determine which of the claimed compounds can be used to treat even one disease caused by bacteria, to say nothing of the considerable number of diseases that one would have to test for therapeutic efficacy against.

It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted; also suggested is that the term "pharmaceutical" be deleted from whichever claims recite it.

*

Claims 17-33 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 20-24 recite the term "deoxopristinamycin IIA". This term may be used, but only if accompanied by a chemical name or structure. While it may be true that applicants can be their own lexicographers in some situations, it is also true that the meaning of the terms must be clear. Currently one could not deduce a structure of "deoxopristinamycin IIA" just from the name. It is suggested that either a structure be provided, or else a detailed chemical name.

- Claim 25 is indefinite as to the objective and conditions of step (a). The claim encompasses process in which the time and conditions are not effective to form a compound of formula I; it is suggested that the claim be amended to recite that time

and conditions are indeed effective in this regard. Claim 25 is also indefinite because it does not require isolation of the final product. If the final product is never isolated, how can it be used? The following format is suggested for process (a) of claim 25:

A process for preparing... comprising ...

(i) reacting a pristinamycin of formula II with an amine of formula III in the presence of a reducing agent for a time and under conditions to form a compound of formula I;

(ii) optionally, treating the compound of formula I with an organic or inorganic acid to form a salt of the compound of formula I; and

(iii) recovering the compound of formula I or a salt thereof.

Applicants have argued that the claim does not recite a use, and so the question of "use" is not relevant to the formulation of claim language. However, the reality is that at the end of the reaction, one will have a round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and perhaps other impurities. One who is in possession of such a mixture is not in possession of the target compound. Applicants have argued that, pursuant to 35 USC 271 (g), a chemist outside the U.S. "might" be able to practice the invention without infringing the claims, as long as they did not isolate the compounds. While there is some mention of 35 USC 271 in the MPEP, it is not apparent where it is stated that foreigners are free to infringe process claims as long as they do not isolate the compounds. Applicants should provide much more information about this statute, if it is going to be used in an argument. Second, it is not apparent how a chemist who is possession of round-bottom flask which contains unreacted starting materials, solvent, the"target" compound, and other impurities is going to use this mixture to inhibit bacteria. Third, even if it is true that 35 USC 271 (g) gives persons outside the US license to infringe process claims as long as they do not isolate the compounds, that does not, in and of itself, make the claimed process definite. The rejection is maintained.

- Claim 26 is indefinite as to the objective and conditions of step (a). The claim encompasses process in which the time and conditions are not effective to form a

compound of formula IV; it is suggested that the claim be amended to recite that time and conditions are indeed effective in this regard. Claim 26 is also indefinite because it does not require isolation of the final product. If the final product is never isolated, how can it be used? The following format is suggested for process (a) of claim 26:

A process for preparing... comprising ...

(i) reacting a pristinamycin of formula II with an amine of formula III for a time and under conditions to form a first intermediate compound of formula IV;

(ii) reacting the first intermediate compound of formula IV with a reducing agent for a time and under conditions to form a compound of formula I;

(iii) optionally reacting said compound of formula I with formaldehyde, or with a compound which generates formaldehyde in situ for a a time and under conditions to form a second intermediate compound, and subsequently reacting said second intermediate compound with a reducing agent to form a compound of formula I ...

(iv) optionally, treating the compound of formula I with an organic or inorganic acid to form a salt of the compound of formula I; and

(v) recovering the compound of formula I or a salt thereof.

- Claim 28 makes reference to a "group B streptogramin derivative". However, further information, such as a chemical name or structural formula, is required. The same applies in the ase of claims 29 and 30.

- Claim 32 characterizes diluents and adjuvants as "agents". However, the term "agent" is normally associated with the biologically active ingredient, rather than the inactive carrier. Accordingly, use of term in this way is misleading. Applicants have argued that claim 32 has been amended. However, there is no directive to amend claim 32 in paper No. 15.

- Claim 32 recites that the presence of diluents and adjuvants is "optional". Note that a composition requires at least two components. Applicants are requested to provide an example of a composition which contains only one pure streptogramin A

derivative, but does not contain either a diluent or an adjuvant. Such an example will provide the basis for further discussion. Alternatively, it is suggested that the claim be amended to make the presence of a diluent or an adjuvant mandatory. In response, applicants have argued that claim 32 has been amended. However, there is no directive to amend claim 32 in paper No. 15.

- Claim 33 recites that the presence of diluents and adjuvants is "optional". This claim differs from claim 32 in that claim 33 mandates the presence of at least two different compounds, and so is clearly a composition in all cases. The issue, however, is what is meant by the term "pharmaceutical composition". Suppose that there are two chemists. The first combines a Group A streptogramin derivative with a Group B streptogramin derivative, and no diluent or adjuvant is added. Similarly, the second chemist combines a Group A streptogramin derivative with a Group B streptogramin derivative, and no diluent or adjuvant is added. Can applicants provide a specific example in which the first chemist would be preparing a "pharmaceutical composition", but the second chemist would only be preparing a "non-pharmaceutical composition"....? It is suggested that the term "pharmaceutical" be deleted from claim 33. In response, applicants have argued that claim 33 has been amended. However, there is no directive to amend claim 33 in paper No. 15.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600